REMARKS

Status of the claims

With entry of the instant amendment, claims 7, 50 and 56 have been amended. The amendments add no new matter.

Claim 7 has been amended to recite that the variable heavy (V_H) chain is covalently linked to the amino terminus of the toxin. Support can be found, *e.g.,* in Fig. 2B and on page 4, lines 15-17; and page 39, lines 28-33.

Claims 1-4, 7-11, 13, 14, 16, 17, and 50-72 are pending in the application. Claims 57-69 are withdrawn by the Examiner. However, as explained below, the withdrawal is improper; accordingly, claims 1-4, 7-11, 13, 14, 16, 17, and 50-72 are properly under examination.

The Examiner's withdrawal of method claims is improper

The Examiner withdrew claims 57-69 from examination as allegedly drawn to a non-elected invention. However, there is no restriction in the application. Although the Office Communication of August 30, 2000 directed Applicants to elect an invention, a subsequent Office Communication dated October 4, 2000 (a copy of which is attached hereto), which provides a summary of an Examiner interview with Applicants' representative, indicated that the restriction would be vacated and an office action on the merits would be forthcoming. In the subsequent Office Action of November 2, 2002, all claims were under examination. Therefore, composition and method claims have been co-examined throughout prosecution. Indeed, as Applicants noted in the response filed March 20, 2006, most of the new method claims (claims 57, 58 59, 60, 61, 62, 63, 64, and 65) submitted in the March 20, 2006 amendment corresponded to method claims 22, 23, 26, 29, 30, 31, 32, 24, and 25 that were cancelled in that same amendment. Claims 22, 23, 26, 29, 30, 31, 32, 24, and 25 all had been under examination. The cancelled claims were presented in the form of new claims 57, 58 59, 60, 61, 62, 63, 64, and 65 simply to make the claim set easier to follow. In view of the foregoing, the Examiner's

withdrawal of claims 57-69 is improper. Applicants therefore respectfully request that claims 57-69 be examined.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 50-56, 71, and 72 are rejected as allegedly not enabled. The Examiner contends that the claims are not enabled because the recited percent identity could encompass variants in which the CDRs contain substitutions. Applicants disagree with the Examiner's analysis of the claims. However, in order to expedite prosecution, the claims have been amended to further emphasize that the claimed RFB4 ds(Fv) molecules have the RFB4 CDR sequences. Although some sequence variation may occur relative to the reference sequences, the claims plainly set out that the (claimed) V_H and V_L regions have the CDRs of SEQ ID NOs. 2 and 4, respectively. This is a distinct element of the claims and a characteristic of the genus of RFB4 ds(Fv) antibodies. In view of fact that the meaning of the claims is unambiguous, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 103

Claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, 50-56 and 70-72 are rejected as allegedly obvious over the various references cited in the Office Action on page 4. Applicants have traversed this rejection for reasons of record.

As previously explained, the law is clear: knowledge of general methods, in this case sequencing V_H and V_L regions of antibodies, does not render any particular sequence obvious. Further, even assuming *arguendo* that the claims could be considered *prima facie* obvious, the claims are patentable due to surprising and superior properties of the claimed RFB4-ds(Fv) immunoconjugates. In the FitzGerald Declaration filed March 11, 2004, Dr. FitzGerald attests to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 IgG is unusual. The Examiner cites Reiter *et al.* (*Biochemistry*) as showing better cytotoxicity of a dsFv compared to an scFv, and as teaching that an scFv can retain the specificity and affinity of IgG. However, there is no reasoning or evidence provided in the rejection as to why one of skill would conclude that the RFB4 antibody-toxin conjugates

claimed here would in fact have these properties. The mere teaching that a composition could possibly have a characteristic does not lead to the logical conclusion that all of such compositions would have that characteristic. Indeed, Dr. FitzGerald explains that typically binding affinity is lowered in such a conjugate in comparison to the parent antibody.

In addition, Dr. FitzGerald explains that the superior toxicity and efficacy of RFB4ds(Fv)-PE38 not only in animal models, but also in human Phase I trials (referring to his previous Rule 1.132 Declaration, signed May 15, 2001, which is of record in this application) was surprising and could not be predicted from the art (sections 9 and 10) of the March 11, 2004 FitzGerald Declaration. Indeed, the clinical trials referred to by Dr. FitzGerald showed that 11 patients achieved complete remission and 2 patient achieved partial remission when RFB4ds(Fv)-PE28 was administered to them (section 10 of the FitzGerald Declaration signed May 15, 2001). Again, the Examiner provides no evidence or reasoning as to why one of skill could predict such superior properties based on the cited art..

The Examiner additionally contends that the claims under examination are drawn to a product, not a method, and that the methods are therefore irrelevant to the examination of the product. However, this is incorrect. The Examiner's withdrawal of the methods claims is improper for the reasons explained above. Accordingly, even assuming *arguendo* that Applicants' evidence of surprising results is not sufficient for the Examiner to deem the compositions as allowable over the art, Applicants have offered ample evidence that the claimed methods of treating B cell malignancies are unobvious over the cited art. Accordingly, minimally, the method claims are patentable.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 50-56 are rejected as allegedly indefinite. The Examiner contends that it is not clear whether the 90% (or 95%) identity extends to the CDRs. Applicants traverse this rejection. The claims plainly state that the V_H and V_L regions have the CDRs of the references

sequences, not CDRs having 90% identity to the reference sequence. Accordingly, the claims are clear. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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